January 7 , 1950.

Dr. L. Cavalli,
Dept. Genetics,
University of Cambridge,
England.

Dear Cavalli:

Thank you for your "123" cultures, which arrived some time ago in excellent condition. I can't recall whether I've mentioned the unlikelihood that the second culture is "Lac3-", owing to its glu+ phenotype. However, I will be glad to try to classify in terms of the arbitrary designations given to our Lac- mutants.

I have tried two crosses with the "123" strain (which I shall record as W-1258). X 677 and X 1178 (the latter is a Mal- mutant from a TLB1-Lac1-$V1^r$ segregant from H-1). The yields were very poor on the first cross, and the background rather heavy. The second came out very well, with good yields of prototrophs, some of which may be diploid, but doubtfully. There were about 1% Lac-, 99% Lac+. Of 100 Lac+, 98 were Mal+$V1^s$ (parental), 1 Mal-$V1^s$, and 1 Mal+$V1^r$. Of 9 Lac-, 5 were Mal+$V1^s$, 3 Mal+$V1^r$, and 1 Mal-V_1^r (par.) There seems to be little question of the validity of recombination between these strains. Some colonies show peculiar mottled appearance on EMB Lac, with a very variable colony size and fermentation intensity on restreaking, and these may conceivably have been diploid, but not yet proven to be.

The most important point that I would like to convey is that W-1258 is very susceptible to the lysogenic phage, lambda, carried by K-12 stocks. Considerable plaquing was observed in the background growth of the cross 1258 x 677, which led to our check on this point. The virus may be an important barrier to hybridization, and may also play some part in the very peculiar segregation ratios observed in these crosses. I am working to secure lambda-resistant or lysogenic 1258 cultures, and will send these promptly if successful.

We have been trying our own hand at determining the nutritional requirements of this culture, and they are very complex indeed. Excellent growth can be obtained on complete media to which a bit of yeast extract is added (.3%). The requirement seems to be for a balanced combination of at least three aminomacids--I hope to have more definite information soon.

I hope you will not think it impertinent if I raise some suggestions concerning your personal plans. Do you have a permament staff appointment now at Cambridge? I think that I would enjoy very much the opportunity of discussions with you at closer range than across the Atlantic, and I wonder if you have given any thought to the desirability of visiting or working at some of the many microbial-genetics laboratories in this country, perhaps on a fellowship basis. Owing to space limitations, we could not accomodate you satisfactorily here for perhaps another 12 or 15 months, but even so, it would not be too early to explore the possibilities, as well as the interest that you might have in such arrangements. In addition, I have been asked for suggestions for potential importations of scientific talent in this field, for fellowships or staff appointments at other universities in this country. Your name has been mentioned, but I have not known whether to press it, because I could not tell whether you would have the slightest interest, on the one hand, nor did I have the most elemantary information [viz., your age, marital status, academic history, present position, etc.] on the other. If you could give me your reactions to these particular points, and to your interest in working in this country, I am sure that something eminently satisfactory might be worked out. Possibly, I am overreaching myself in raising this question, but please be assured that there is no matter of patronisation, but only my hope for a closer convergence of our related interests.

To close on a scientific note, we have been doing some UV experiments on heterozygous diploids. The only prominent effect is the apparent "conversion" of diploid to haploid (i.e. cells which would form mosaic colonies to cells which form only pure colonies). No balanced lethal diploids have been found, nor have partial losses (i.e., pure for one factor; segregating for others). The analysis will be very complex, owing to the multinucleate character of diploid and haploid cells; we are concentrating now on the genetic effects of very low doses (with negligible killing), to determine whether the shoulder or threshold region of the UV sterilization curve has genetic effects, which is to say, whether it is actually due to genetic (nuclear?) reduplication. I have been told that the reported linear kinetics of UV killing even in E may be fallacious; it certainly does not hold with K-12 or with the diploids. Since segregations occur uncontrollably (arguing from the absence of balanced heterozygotes on complete medium), the model may be a multinucleate cell the sterilization of which requires a lethal hit (not necesaarily homologous) in each nucleus. Even if the lethal mutations are recessive, and the cell is not "killed" thereby, it will be sterilized since the heterokaryotic (or heterogenic) conditions is not maintained (as it is e.g. in Neurospora). This may mean that minimal medium, on which the equivalent of lethals (viz. nutritional requirements) are maintained balanced, actually maintains the diplophase by more than merely selecting for it, or to state the converse, that complete medium actually induces segregation. This is being tested. This conclusion assumes that lethal mutations should have been induced in diploids with UV dosages which induce substantial killing.

Sincerely,

Joshua Lederberg